REMARKS

Claims 4, 7, 10-11, 14, 17-22, 26-28, 31, 41, and 43-64 are pending in this application. Claims 4, 7, 10-11, 14, 17-22, 26-28, 31, 41, and 43-64 have been canceled. New claims 65-67 have been added. The new claims find support in the specification and original claims, for example, in original claim 7 (compound in new claim 65); in original claim 27 (pharmaceutical composition); and at page 3, lines 27-30, at page 4, lines 19-22 and at page 10, lines 14-17 (methods of lowering free fatty acids in an individual). No new matter has been added. After entry of this amendment claims 65-67 will be pending in this application.

Applicants thank the Examiner for withdrawing the rejection under 35 U.S.C. § 112, ¶ 2.

I. The Claims Are Enabled

A. Methods of Lowering Free Fatty Acids (New claim 67)

Claims 28-31 are rejected under 35 U.S.C. § 112, ¶ 1, as allegedly failing to satisfy the enablement requirement. The Office alleges that the "methods of treating a metabolic-related disorder and raising HDL" are not enabled. However, claims reciting methods of treating metabolic-related disorders and raising HDL were canceled in the response filed on December 17, 2008. Further, Applicants have canceled the previously presented claims and have added new claims 65-67. New claim 67 recites a method of lowering free fatty acids in an individual using 3-(1H-tetrazol-5-yl)-2,4,5,6-tetrahydro-cyclopentapyrazole, or a pharmaceutically acceptable salt, solvate or hydrate thereof.

Applicants respectfully assert that new claim 67 is fully enabled. In their response filed on August 19, 2009, Applicants referred the Office to a statement on page 57 of the specification, which states:

> Certain compounds of the invention have an EC_{50} in the ^{3}H-nicotinic acid binding competition assay within the range of about 10 to about 100 μM. More advantageous compounds of the invention have an EC_{50} value in this assay within the range of about 1 to about 10 μM. Still more advantages compounds have an EC_{50} value in this assay of less than about 1 uM.

Further, the specification teaches that the compounds are active in a functional *in vitro* GTPγS binding assay (specification, page 52, lines 28-31). The Office refuses to consider this data, alleging that the specification is "vague and it is unclear which compounds have the EC50 data" (Office Action, page 3, *sic*). The Office is reminded that it is required to "back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement". *In re Marzocchi*, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971). The Office provides no evidence to why one of ordinary skill in the art would refuse to accept that the EC_{50} values in the specification relate to examples of the specification, such as the single species recited in new claim 67.

However, solely to advance prosecution, Applicants refer the Office to Semple, et al., "3-(1H-Tetrazol-5-yl)-1,4,5,6-tetrahydro-cyclopentapyrazole (MK-0354): A Partial Agonist of the Nicotinic Acid Receptor, G-Protein Coupled Receptor 109a, with Antilipolytic But No Vasodilatory Activity in Mice", *J. Med. Chem.* 51:5101-5108 (2008) ("Semple"); and Lai, et al., "Effects of a Niacin Receptor Partial Agonist, MK-0354, on Plasma Free Fatty Acids, Lipids, and Cutaneous Flushing in Humans", *J. Clinical Lipidology* 2(5):375-383 (2008) ("Lai") (enclosed for the Office's convenience). Semple discloses that the species in new claim 67, referred to as compound **5a** or MK-0354, is a partial agonist at the hGPR109a (RUP25) receptor (see EC_{50} values in Table 1, page 5103). Further, MK-0354 had an EC_{50} of 2.3 μM in a hGPR109a (GTPγS assay), with an efficacy of 72% of nicotinic acid (Semple, page 5103, column 1). In binding studies, compound **5a** (MK-0354) was also found to be a competitive inhibitor of ^3H nicotinic acid binding to hGRP109a (**5a** K_i = 505 nM; nicotinic acid K_i = 50 nM) (Semple, page 5103, column 1). Further, compound **5a** (MK-0354) was found to be "similar in efficacy and marginally more potent than nicotinic acid" in lowering free fatty acids in plasma in mice (Semple, page 5103, column 2, Figure 1). In the free fatty acid plasma test, the "time course of the nicotinic acid-induced plasma FFA reduction was determined in a mouse, and dose-response experiments with **5a** were performed at a single time point (20 min), the time of maximum efficacy of nicotinic acid in this model" (Semple, page 5103, column 2). Hence, Semple clearly demonstrates that the compound **5a** (MK-0354) can lower free fatty acids in

mice. Further, Lai shows that MK-0354 can also lower free fatty acids in humans. For example, Lai discloses that "[a]dministration of MK-0354 single doses up to 4000 mg and multiple doses (7 days) up to 3600 mg produced significant dose-related reductions in plasma FFA" in Phase I clinical trials (see Lai, page 381; and abstract). This evidence clearly demonstrates that the method of lowering free fatty acids in an individual using MK-0354, as recited in new claim 67, is fully enabled. Applicants, therefore, respectfully request that all of the requirements of 35 U.S.C. § 112, first paragraph, have been met and request that the rejection be withdrawn.

In addition, Applicants wish to clarify the record. In one of their previous responses, Applicants stated that:

> (1) nicotinic acid was known to have activity in lowering triglycerides and free fatty acids as recited by the claims; (2) the murine variant of the known RUP25 receptor was shown to mediate the metabolic effects of nicotinic acid; (3) nicotinic acid was known to bind to and agonize the RUP25 receptor; and (4) the novel claimed compounds of Formula (I) also bind to and agonize the RUP25 receptor. As a result, one of skill in the art would recognize that an agonist of the RUP25 receptor, such as the compounds recited by the methods of claims 28 and 31, would be expected to have efficacy in lowering triglycerides and free fatty acids as does nicotinic acid.

However, while MK-0354 was shown to lower free fatty acids in Phase I clinical trials, Lai also discloses that "4 weeks treatment of MK-0354 failed to produce changes in high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, or triglycerides" in Phase II clinical trials (see Lai, abstract). Applicants, therefore, have canceled previously presented claim 28, reciting a method of lowering triglycerides in an individual, and further bring this fact to the Examiner's attention for the sake of clarity.

B. Solvates and Hydrates

Claims 4, 7, 10, 11, 14, 17-22, 26-28, 31, and 41 are rejected under 35 U.S.C. § 112, ¶ 1, for allegedly failing to comply with the enablement requirement with regard to the solvates and hydrates of the claimed compounds. As a preliminary matter, Applicants have canceled the

previously presented claims and have added new claims 65-67, reciting a single species, 3-(1H-tetrazol-5-yl)-1,4,5,6-tetrahydro-cyclopentapyrazole (MK-0354).

The Office improperly relies on its own presentation at the March 12, 2008 Biotechnology, Chemical, and Pharmaceutical Customer Partnership Meeting for its factual and legal positions (Office Action, pages 4-5). As the presentation was made after the filing date of present application, the Office is reminded that post-filing date references should not be used to support an enablement rejection. M.P.E.P. § 2164.05(a). Further, the Office's statements in a presentation without citation to any scientific authority are not facts. Finally, the Office's legal opinions in a presentation are not legal authority. Applicants, therefore, object to the use of this presentation as a proper basis for a rejection under 35 U.S.C. § 112, ¶ 1.

Citing to its own presentation, the Office states that enablement requires disclosure of "the identity and location of modifications to the compound", because "[i]t is known that crystalline states of compounds such as solvates and hydrates can undergo phase transformation and that an exact disclosure of the changes should be disclosed" (Office Action, page 5). First, Applicants again object to the Office's use of its own presentation as support for the enablement rejection. Second, Applicants are claiming general "solvates" and "hydrates" of an individual species. Applicants are not claiming *specific* types of hydrates or solvates (e.g., a dihydrate or monohydrate, or a particular polymorph) and, therefore, there is no need to disclose the "identity and location of modifications".

Further, according to the Office, the solvates and hydrates are not enabled because the "instant specification does not have any working examples of solvates and hydrates". However, there is no requirement for working examples where, as here, persons skilled in the art would otherwise be able to practice the claimed invention. *In re Borkowski*, 164 U.S.P.Q. 642, 645 (C.C.P.A. 1970). Indeed, in *Atlas Powder Company v. E.I. Du Pont De Nemours & Company*, the court found a broad claim enabled even without a large number of working examples. 224 U.S.P.Q. 409, 413-414 (Fed. Cir. 1984). In *Atlas Powder*, the defendant alleged that the specification disclosed "numerous salts, fuels, and emulsifiers that could form thousands of emulsions but there is no commensurate teaching as to which combination would work". *Id.* at

413. Therefore, the defendant alleged that the disclosure was "nothing more than 'a list of candidate ingredients' from which one skilled in the art would have to select and experiment unduly to find an operable emulsion". *Id.* at 413. The court disagreed, noting that the burden was on the defendant to show non-enablement. *Id.* at 414. *See also*, M.P.E.P. § 2164.08(b) (stating that the "presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled" and that the "standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art").

In the present application, claim 65 recites solvates and hydrates of only a single species, and its pharmaceutically acceptable salts. As summarized in the prior responses, the art suggests that hydrates and solvates form quite readily for many pharmaceutically active compounds.[1] Moreover, there are well-established and routine methods for screening compounds for solvate and hydrate formation.[2] Even a considerable amount of experimentation will not be considered undue, if it is merely routine. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)). However, as discussed above, the experimentation for the present case is far from considerable, as a person of ordinary skill could readily screen the single species of new claim 65 and its pharmaceutically acceptable salts using the well-known and routine screening methods for solvate and hydrate formation. The Office has not explained why this routine experimentation is somehow "undue experimentation".[3]

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[1] For example, at least one reference states that "[m]ost organic and inorganic compounds of pharmaceutical relevance can exist in one or more crystalline forms" and that "approximately one-third of the pharmaceutically active substances are capable of forming crystalline hydrates". See e.g., Vippagunta, "Crystalline Solids", Advanced Drug Delivery Reviews, 48: pages 4 and 15 (2001) (emphasis added).

[2] See e.g., Guillory, "Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids", in Polymorphism in Pharmaceutical Solids, ed. Harry G. Brittain, vol. 95, chapter 5, Marcel Dekker, Inc., New York 1999, pages 183-226 (hereinafter "Guillory") at pages 202-205 and pages 205-208, describing the routine preparation of hydrates and solvates of compounds.

[3] The Office also states that working examples are needed to "determine whether the instantly claimed compounds can be solvates and hydrates and *what the pharmacological properties would be*" (Office Action, page 6, emphasis added). In clear contravention of *In re Marzocchi*, the Office has provided absolutely no reasoning or evidence of why solvates and hydrates of MK-0354 would not be expected to show the same ability to lower free fatty acids in an individual as does MK-0354.

When all of the evidence is considered, the claimed solvates and hydrates are enabled. As the court in *In re Marzocchi* stated, it is "incumbent upon the Patent Office...to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement". 169 U.S.P.Q. at 370 (emphasis added). The Office has provided no acceptable evidence for its allegation that a person of skill in the art could not make and use the solvates and hydrates of the claimed compounds without undue experimentation. Applicants, therefore, respectfully assert that all of the requirements of 35 U.S.C. § 112, ¶ 1, have been met and request that the claim rejection be withdrawn.

III. Supplemental Information Disclosure Statement

Applicants submit a supplemental information disclosure statement herewith for consideration by the Examiner.

IV. Conclusion

Applicants respectfully assert that rejections of record have been overcome by way of this response. Allowance of all claims is respectfully requested. The Examiner is urged to contact Applicant's undersigned representative at (302) 778-8411 if there are any questions regarding the claimed invention.

The Commissioner is hereby authorized to debit any fee due or credit any overpayment to Deposit Account No. 06-1050. Further, if not accompanied by an independent petition, this paper constitutes a Petition for an Extension of Time for an amount of time sufficient to extend the deadline if necessary and authorizes the Commissioner to debit the petition fee and any other fees or credit any overpayment to Deposit Account No. 06-1050 referencing attorney docket no. 22578-0005US1.

Respectfully submitted,

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Enclosures: Semple and Lai references
Supplemental Information Disclosure Statement
Petition for Extension of Time (3-months)

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